REMARKS

In response to the objections raised by the Examiner in the April 27, 2001 Office Action, our comments follow. Reconsideration and withdrawal of the restriction requirement are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance.

I. STATUS OF CLAIMS

Claims 7-25 and 27-41 are currently pending in this application. No new matter is added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, any amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support for any amendments is found throughout the specification and from the pending claims.

II. RESPONSE TO RESTRICTION REQUIREMENT

The April 27, 2001 Office Action required an election under 35 U.S.C. § 121 from among:

Group I. Claims 1-6, and 27-32, drawn to a method of immunotherapy using a *Notch* ligand, classified in class 514, subclass 2;

Group II. Claims 7-12, drawn to a method of tolerizing T cells to an antigen or allergen using *Notch*-ligand expressing antigen presenting cells (APCs), classified in class 435, subclass 373;

Group III. Claims 13-18, drawn to notch ligand conjugates and a kit comprising *Notch* protein or family members, classified in class 530, subclass 350 and class 435, subclass 810;

Group IV. Claim 19, drawn to an assay determining the effect of a compound on ligand binding to *Notch*, classified in class 436, subclass 501;

Group V. Claim 20, drawn to a *Delta* or *Serrate* ligand, classified in class 530, subclass 350;

Group VI. Claim 21, drawn to an assay for free *Serrate*, *Notch* or *Delta* family members *in vivo*, classified I class 424, subclass 9.1;

Group VII. Claim 22, drawn to an assay for determining a compound's effect on *Notch* or ligand expression, classified in class 435, subclass 6;

Group VIII. Claim 23, drawn to compounds which affect *Notch* or ligand expression, classified in class 536, subclass 24.5; and

Group IX. Claims 24 and 25, drawn to a compound which down regulates *Delta* or *Serrate* expression, classified in class 536, subclass 24.5.

The invention of Group I, Claims 1-6, and 27-32, drawn to a method of immunotherapy using a *Notch* ligand, classified in class 514, subclass 2 are again elected, and the previous election of this Group confirmed, with the Examiner again thanked for appreciating that there had been a misunderstanding between the Examiner's understanding of that which Applicants had elected in the Applicants' initial election and the Applicants' understanding of that which Applicants had elected in Applicants' initial election, and the Examiner's gracious withdrawal of the first Office Action on the merits in view thereof. Again, the Examiner's actions were greatly appreciated and were in the spirit of helping the Applicants toward getting a patent. The undersigned heartily commends the Examiner for his actions and welcomes the opportunity to further state such to the PTO.

III. RESPONSE TO ELECTION REQUIREMENT

The April 27, 2001 Office Action further required an election of species from among: allergy, autoimmunity, graft rejection, tumor-induced aberrations and infectious disease. Accordingly, within Group I, species a, allergy, is elected, with traverse, for further prosecution in this application. Reconsideration and withdrawal of the species election requirement are respectfully requested in view of the remarks herewith.

Initially, with respect to the traverse, it is hereby directly stated that Applicants are not making any admissions concerning the separate patentability of the individual species, each as to the other and each as to the more general T-cell mediated disease or infection; and, each of the individual species may be patentably distinct each as to the other and each as to the more general T-cell mediated disease or infection. But, this does not mean that all, or more than one of, species

cannot be examined and searched together in this application, without any undue or serious burden on the Examiner, especially in view of the data presented herewith demonstrating the invention in various species.

Turning to the Office Action, it states that "the species are distinct, one from another, because each type of condition requires response from different subsets of immune cells which require different suppression or activation for treatment of the condition". Office Action, at 4. However, it is respectfully submitted that no support is cited for this statement. In addition, the presently elected aspect of the invention relates to a method of treating T-cell mediated disease or infection. The instant invention relates to a common mechanism (Notch signaling), which underlies all of the specific individual indications listed, and others as well. This common mechanism of action provides the necessary unity of invention under 35 U.S.C. 121. As the invention provides a common principle, it is appropriate for the invention to be claimed accordingly, so that the claims properly reflect the contribution made by the invention.

It is understood that the Examiner can broaden the search to include other species, e.g., upon determining that a species is allowable, or as discussed herein, when there is a relationship among the species and/or number of species is not too great. In this regard, the Examiner is respectfully requested to review M.P.E.P. § 808.01(a), which states that "where there is no disclosure of relationship between species (*see* M.P.E.P. §806.04 (b)), they are independent inventions and election of one invention" is required (July 1998). In view of M.P.E.P. §803, however, when the generic claim includes sufficiently few species that a search and examination of all the species at one time would not impose a serious burden on the examiner, then a requirement for election is inappropriate. To assist the Examiner in examining more than one species, new claims herewith present various species or combinations of species. No new matter is added; and, the new claims herewith are presented without prejudice, without admission, without surrender of subject matter, without any intention of creating any estoppel as to equivalents, not in reply to any art or other rejections under Sections 101, 102, 103 and 112 and are presented to merely round out the scope of protection to which Applicants are entitled.

In the instant case, there is a disclosure of relationship between the claimed species. The claims are directed to, *inter alia*, the use of therapeutic compounds that modify T cell activity by

modulating the interaction between *Notch* protein family members and their ligands. Unity of invention, therefore, exists.

Allergy, autoimmunity, graft rejection, tumor-induced aberrations and infectious disease are a discrete class of conditions, limited in number, that may be treated by therapeutic compounds that modulate T cell activity. In fact, all the conditions are the result of T-cell reactions to foreign or self-antigens.

Applicants have data attached demonstrating that Notch ligands can be used to control T-cell activity in a uniquely antigen-specific manner. A range of different antigens was used to show that the mechanism involved relates to underlying T cell activity, and is not restricted to any particular disease or indication. To summarize, these data, together with the examples already presented in the present application, show that Notch ligands can be used to control T-cell activity *in vitro* and *in vivo*, including mouse and human cells, and with a wide range of very different antigens (including Der p1 from the human Dust mite, Haemagglutinin (HA) from the influenze virus and whole allograft cells from mice). This shows that the principle involved is of entirely general application. Moreover the range of different antigens used shows that the mechanism involved relates to underlying T-cell activity and is not restricted to any particular disease or indication as such. If called upon by the Examiner, a Declaration containing this data will be submitted as additional evidence (e.g., Declaration form) for the general application of the invention.

A search and examination of the methods of treatment would not impose a serious burden on the examiner as the search and examination could be directed to the underlying mechanism of the Notch signaling pathway.

Accordingly, reconsideration and withdrawal, or at least a restructuring of the election of species requirement are respectfully requested.

IV. CONCLUSION

It is respectfully submitted that the results of the present election of species requirements are inefficiencies and unnecessary expenditures by both the Applicants and the PTO and extreme prejudice to Applicants (particularly in view of GATT, a shortened patent term may result in any divisional applications filed); and restriction has not been shown to be proper, especially since

there is no serious burden in examining and searching all five species and there are relationships among the five species. Indeed, the search and examination of each species is likely to be co-extensive and, in any event, would involve such interrelated art that the search and examination of the entire subject matter of Group I can be made without undue burden on the Examiner. All of the preceding remarks, therefore, mitigate against restriction.

In view of the foregoing, reconsideration and withdrawal of the election of species requirements and favorable examination of Claims 27-40 on the merits are respectfully requested, especially in view of the data herewith; and, if the Examiner would like a Declaration containing the data prior to any office action on the merits, or would otherwise wish to discuss the case, e.g., with a view towards recognizing allowable subject matter or otherwise expediting prosecution, the Examiner is invited to contact the undersigned by telephone for an interview at a time and in a manner convenient for the Examiner, who is again thanked for the many courtesies he has already extended during this prosecution.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants(s)	:	Lamb et al.
U.S. Serial No.	:	09/310,685
Filing Date	:	May 4, 1999
Examiner	:	F. Pierre Vandervegt, Ph.D
Art Unit	:	1644
For	:	**NOTCH**

745 Fifth Avenue
New York, NY 10151

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on July 27, 2001.

AMY LEAHY, REG. NO. 47,739
Name of Applicant, Assignee or Registered Representative

Amy Leahy for Thomas J. Kowalski Reg. No. 32,147
Signature

July 27, 2001
Date of Signature

DATA ATTACHMENT TO
RESPONSE TO OFFICE ACTION WITH AMENDMENT,
REQUEST FOR EXTENSION OF TIME AND
WITHDRAWAL OF RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is in also in response to the Office Action dated April 27, 2001.

In order to demonstrate further the use of Notch ligand in the control T-cell mediation of immune responses, the following studies have been carried out by Applicants or Applicants' assignee, in the ordinary course of business.

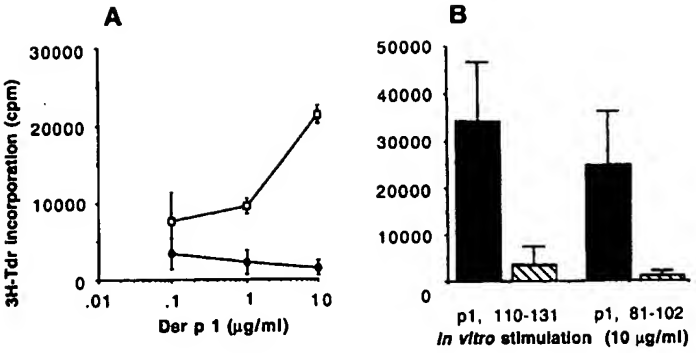
Study 1

Notch ligand expressing antigen-presenting cells
inhibit T-cell immunity to the antigen presented.

(A) Mouse antigen-presenting cells (APC) were infected with Notch ligand gene *Serrate1* (•) or control (□) virus, pulsed with dust mite antigen p1, 110-131 peptide and injected into naïve C57BL/6J mice and two weeks later mice were immunized with 50 μg House Dust Mite (HDM) antigen Der p 1/Complete Freund's Adjuvant (CFA). Lymph node (LN) cells were cultured *in vitro* with Der p 1 and T-cell proliferation was measured and the results presented as mean c.p.m. ± SD of four mice per group.

(B) LN cells from mice primed as described above [*Serrate1*$^+$ APC (shaded bars) or a control APC (closed bars)] were cultured *in vitro* with the Der p1 peptides p1, 110-131 or p1, 81-102 at 10μg/ml and proliferation measured. The supernatants from these assays were collected at 24 h and assessed for IL-2 production (C), while 48 h supernatants were assessed for the presence of IFN-γ (D).

This study shows that antigen-presenting cells expressing Notch ligand are able to inhibit T-cell activity to antigen.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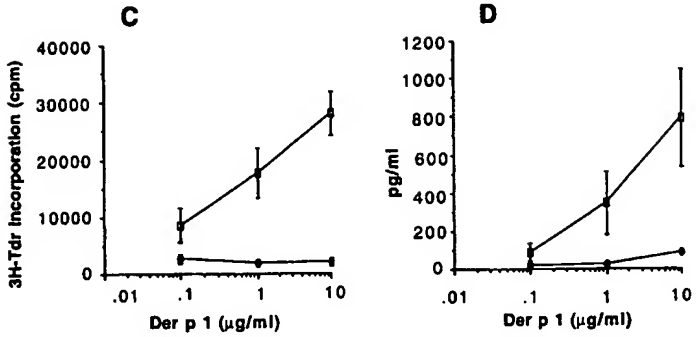
p1, 110-131
p1, 81-102
in vitro stimulation (10 µg/ml)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Der p 1 (µg/ml)
D
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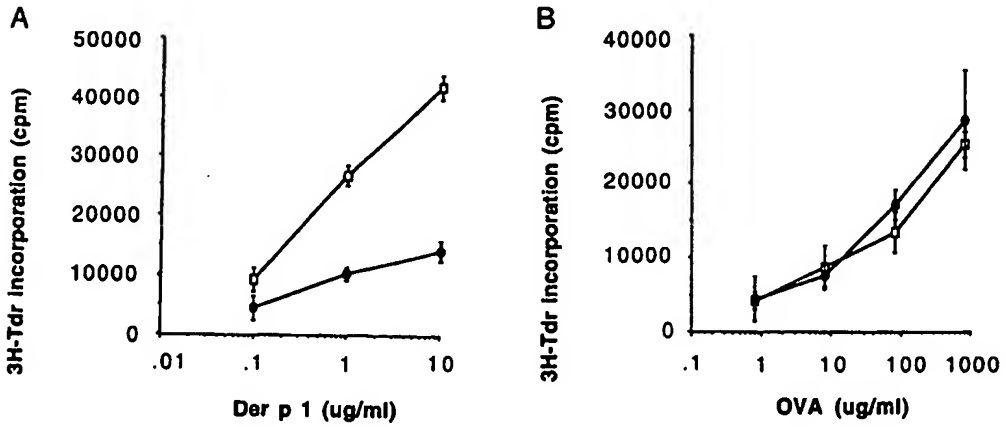
1000
800
600
400
200
0
pg/ml
.01
.1
1
10
Der p 1 (µg/ml)

Study 2

Immunization with Notch ligand expressing antigen-presenting cells pulsed with specific peptide induces antigen specific but not global suppression of immunity.

(A) APC were infected with *Serrate1* (•) or control (□) virus pulsed with p1, 110-131 and 2 weeks later the mice were immunized with 50 μg Der p 1/CFA. LN cells were cultured *in vitro* with Der p 1 and proliferation was measured and the results presented as mean c.p.m. ± SD of four mice per group. (B) Mice were injected with *Serrate1*$^+$ APC pulsed with p1, 110-131 as described above but then immunized with OVA/CFA. LN cells were re-stimulated with OVA *in vitro* and proliferation measured as above.

This study shows that antigen-presenting cells expressing Notch ligand in the context of one antigen are able to inhibit the immune response in relation to that specific antigen, but without global suppression of immunity (ie immune response to other antigens, such as the ovalbumin used here, is not significantly affected).



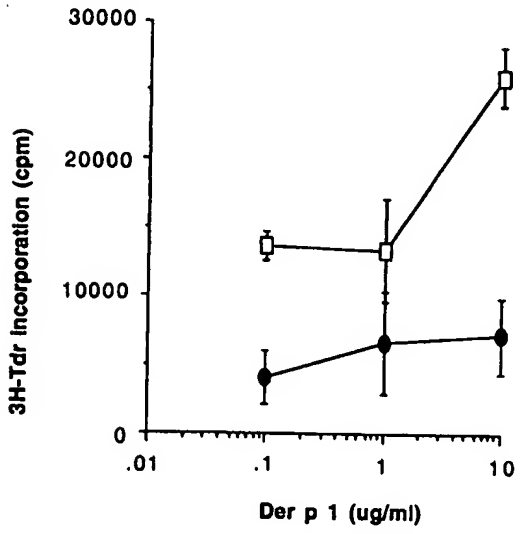
These experiments showed the ability of Notch ligand to induce tolerance in a prophylactic protocol. However, Notch ligand can also induce tolerance to an established immune response as shown in Study 3 below.

Study 3

Notch ligand expressing antigen-presenting cells inhibit established immune responses.

Naïve mice were immunized with 50 μg Der p 1/CFA and 3 weeks later they were injected with p1, 110-131-pulsed DC infected with either *Serrate1* (•) or control (□) virus. Two weeks later mice were reimmunized with 50 μg Der p 1/incomplete Freund's adjuvant and the proliferative response of LN cells to re-stimulation with Der p1 measured as described in Study 1 (A) above.

This study shows that Notch ligand can also induce tolerance to an established immune response.

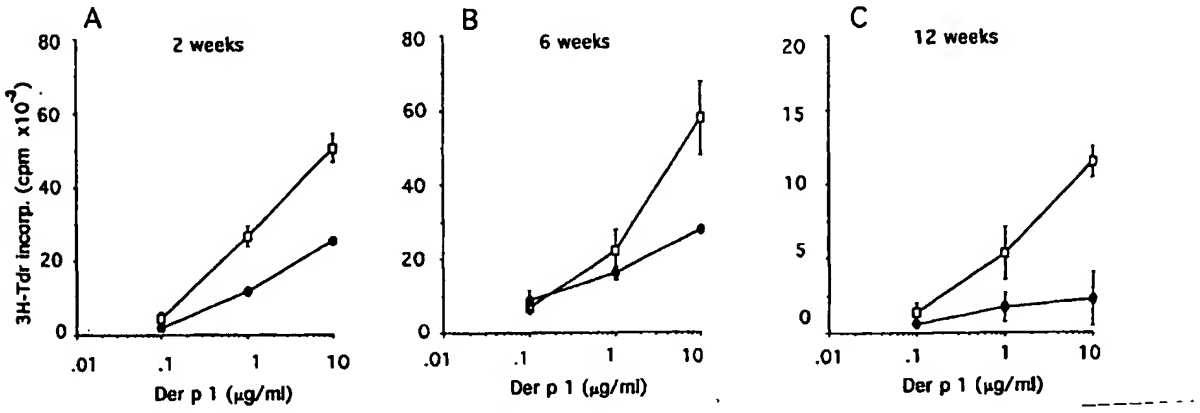


Study 4

Inhibition of T-cell responses induced by Notch ligand expressing antigen-presenting cells is long lived.

p1, 110-131 peptide-pulsed APC infected with either *Serrate1*$^{+}$ (•) or control (□) virus were injected into naïve C57BL/6J mice and (A) 2, (B) 6 or (C) 12 weeks later mice were immunized with Der p 1/CFA and proliferation determined as described in Study 1(A) above.

This study shows that Notch ligand inhibition of T-cell responses is long lived.



Study 5

Antigen-specific tolerance induced by Notch ligand expressing antigen-presenting cells can be transferred to naïve mice by T-cells.

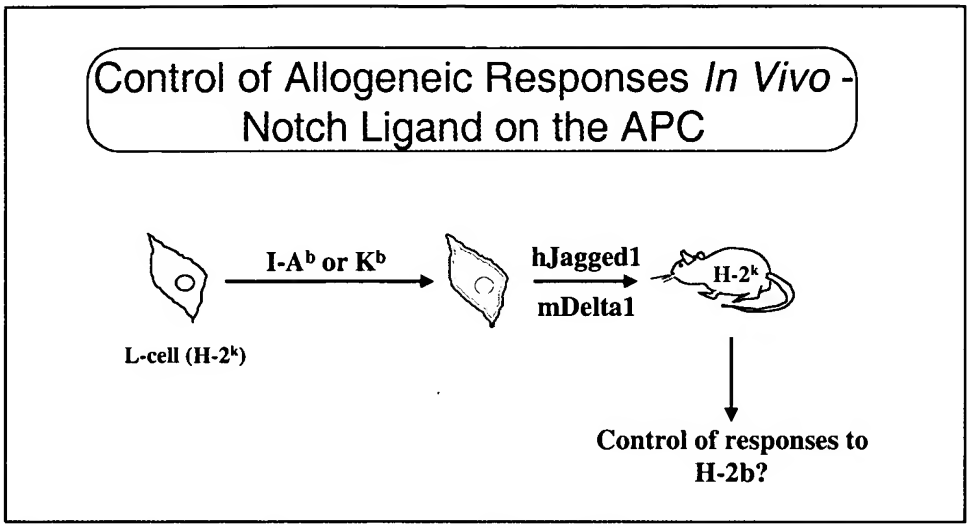
(A) p1, 110-131 peptide-pulsed APC infected with either *Serrate1* or control virus were injected into naïve C57BL/6J mice and two weeks later CD4+ or CD8+ T cells were isolated from spleens and adoptively transferred to naïve mice at 2 x 10^7/mouse. On the same day mice were immunized with 50 μg Der p 1/CFA and 1 week later LN cells were cultured *in vitro* with Der p 1. Results are presented for proliferation (mean c.p.m ± SD of four mice per group) measured at 72 h in response to re-stimulation with 10 μg/ml Der p1. Transfer of T-cells from mice injected with *Serrate 1*$^+$ (open and shaded bars) or control, (solid and grey bars) DC is shown.

(B) p1, 110-131 peptide-pulsed APC infected with *Serrate1* (grey bars) or control (solid bars) virus were injected into naïve C57BL/6J mice and two weeks later CD4+ = T cells were isolated from spleens and transferred to naïve mice (2x10^7 control CD4+ T cells or 2 x 10^7, 5 x 10^6 or 1 x 10^6 CD4+ T cells from *Serrate 1*$^+$ APC injected mice) which were immunized with 50 μg Der p 1/CFA on the same day. Results are presented for proliferation of LN cells (mean c.p.m. ± SD of four mice per group) measured at 72 h in response to re-stimulation with 10 μg/ml Der p1. (C) p1, 110-131 peptide-pulsed APC infected with *Serrate1* (open bars) or control (solid bars) virus were injected into naïve C57BL/6J mice and 2 weeks later CD4+ T cells were isolated from spleens and 2 x 10^7 cells transferred to naïve mice which were immunized with 50 μg Der p1/CFA or OVA/CFA on the same day. Results are presented for proliferation of LN cells (mean c.p.m. ± SD of four mice per group) measured at 72 h in response to re-stimulation with 10μg/ml Der p1 or 800 μg/ml OVA.

This study shows that antigen-specific tolerance induced by Notch ligand can be transferred to naïve mice by T-cells (infectious tolerance).

Study 6

L-cells are a mouse cell line expressing the H-2^k MHC haplotype. These cells were transfected with Class I or class II MHC molecules of the H-2^b haplotype and then further transfected with the Notch ligands Jagged or Delta. These cells were then injected into H-2^k mice to see if they would tolerise the mice to a subsequent transplant of H-2^b cells.

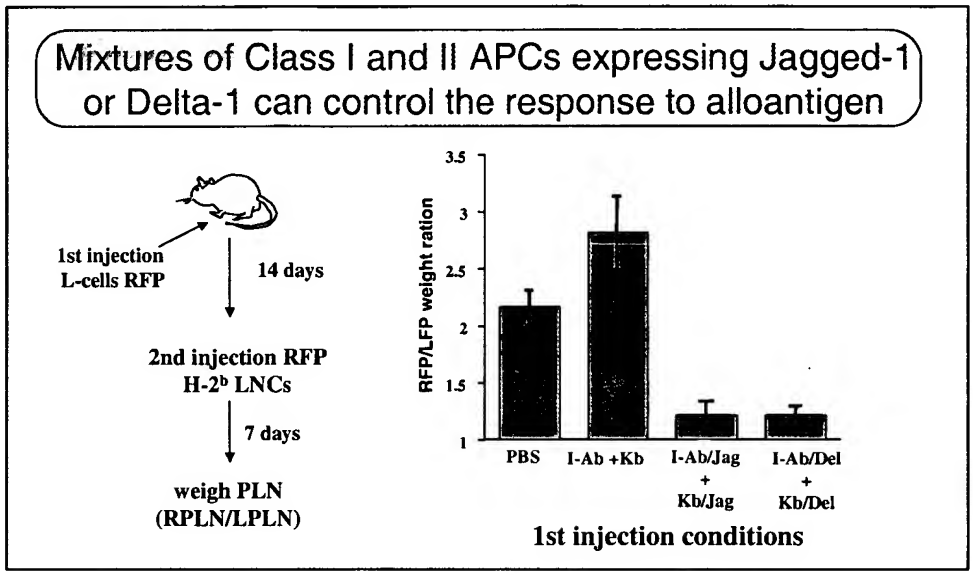


The modified L-cells were injected into the right foot pad of an H-2^k mouse. 14 days later lymph node cells from an H-2^b mouse where injected into the right foot pad. After a further 7 days the popliteal lymph nodes (PLN) draining the right (R) and left (L) feet were removed and weighed and the R/L weight ratio calculated as a measure of the immune response to the transplanted cells. In the first injection the mice received either:

- saline control (PBS)
- the I-A^b & K^b transfected L-cells
- the I-A^b + Jagged & K^b + Jagged transfected L-cells
- the I-A^b + Delta & K^b + Delta transfected L-cells

It is clear from the results below that the Notch ligands have almost completely suppressed the immune response to a subsequent challenge with "foreign" cells. Further studies have shown

that this tolerance is long-lived and specific. The H-2^k-mice tolerised to H-2^b will mount a perfectly normal immune response when challenged with cells from a third strain of mice (H-2^s haplotype).



Summary

To summarise, taken together with the examples already presented in the present application, these results show that Notch ligands can be used to control T-cell activity in a uniquely antigen-specific manner. The same effect has been demonstrated *in vitro* and *in vivo*, in mouse and human cells, and with a wide range of very different types of antigens including:

- soluble antigens (Der p1 and individual epitopes thereof from the House Dust Mite);
- capsid antigen (Haemagglutinin (HA) from the influenza virus); and
- whole allograft cells from mice displaying a range of cell surface antigens in the form of Class I and Class II MHC molecules presenting a range of cellular and exogenous peptides.

This shows that the principle involved is of entirely general application. Moreover the range of different antigens used shows that the mechanism involved relates to underlying T-cell activity and is not restricted to any particular disease or indication as such.

Respectfully submitted,

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